

Could Low Birth Weight be Associated with Cardiovascular Disease in Adolescence?

Poderia o baixo peso ao nascimento ser associado com risco cardiovascular na adolescência?

Priscila de Jesus dos Santos Alves¹ Edward Araujo Júnior² Ana Ciléia Pinto Teixeira Henriques¹
Francisco Herlânio Costa Carvalho³

¹ Department of Community Health, Escola de Medicina, Universidade Federal do Ceará, Fortaleza, CE, Brazil

² Department of Obstetrics, Escola Paulista de Medicina, Universidade Federal de São Paulo, São Paulo, SP, Brazil

³ Department of Maternal and Child Health, Escola de Medicina, Universidade Federal do Ceará, Fortaleza, CE, Brazil

Address for correspondence Edward Araujo Júnior, MD, PhD, Rua Napoleão de Barros, 875, Vila Clementino, São Paulo, SP, Brazil 04024-002 (e-mail: araujojred@terra.com.br).

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Abstract

Purpose Previous studies have shown that low birth weight (LBW) is associated with cardiovascular risk in late adulthood. Recent studies in adolescents suggest that modifiable factors may have greater influence on increased cardiovascular risk. This study aims to investigate the association between LBW and changes in anthropometric and biochemical risk factors during adolescence in a population with low average socioeconomic status.

Methods In a retrospective double cohort, data of birth weight were extracted from hospital records of children born on the same day between 1992 and 2002. According to the World Health Organization, we classified the children as having LBW or normal birth weight. A total of 172 subjects among children, adolescents and adults were researched. We measured anthropometric and clinical data, lipid profile and glucose after an overnight fasting. The low and normal weight groups were compared using Mann-Whitney U, Fischer exact, Chi-square (χ^2) and Student's t tests.

Results Pregnant women with preeclampsia delivered more newborns with LBW ($p < 0.001$). Anthropometric and clinical parameters were similar between groups. No differences were found in the family history of cardiovascular diseases ($p = 0.1$), family incomes ($p = 0.8$) and maternal school education ($p = 0.8$) between groups.

Conclusion In this study, LBW did not increase cardiovascular disease risk factors in adolescents. We observed absence of association between low birth weight and poor health outcomes among adolescents with low socioeconomic status from an urban city in the Brazilian northeast.

Keywords

- low birth weight
- cardiovascular disease risk factors
- anthropometry
- low socioeconomic status
- adolescence

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Resumo

Palavras-chave

- baixo peso ao nascimento
- risco cardiovascular
- antropometria
- baixo nível socioeconômico
- adolescência

Objetivo Estudos mostram que o baixo peso ao nascer está associado ao risco cardiovascular na idade adulta. Estudos recentes em adolescentes sugerem que fatores modificáveis podem ter grande influência no aumento do risco cardiovascular. Este estudo busca investigar a associação entre baixo peso ao nascer com mudanças nos fatores de risco antropométricos e bioquímicos durante a adolescência em uma população com baixo nível socioeconômico.

Métodos Em um estudo retrospectivo de coorte, dados de peso ao nascimento foram extraídos de registros de hospitais, de crianças que nasceram no mesmo dia, entre 1992 e 2002. De acordo com a Organização Mundial da Saúde, classificamos as crianças como baixo peso e peso normal. Um total de 172 pessoas, com idades entre 10 e 20 anos, foram pesquisadas. Avaliamos dados clínicos e antropométricos, perfil lipídico e glicemia de jejum. Os grupos de baixo peso e de peso normal foram comparados pelos testes de Mann-Whitney, Exato de Fisher, Qui-quadrado e t-Student.

Resultados Gestantes com pré-eclâmpsia tiveram mais partos de recém-nascidos com baixo peso ($p < 0,001$). Parâmetros clínicos e antropométricos foram similares em ambos os grupos. Não houve diferença na história familiar de doença cardiovascular ($p = 0,1$), renda familiar ($p = 0,8$) e nível educacional materno ($p = 0,8$) entre os grupos.

Conclusão Neste estudo, o baixo peso ao nascimento não aumentou o risco de doença cardiovascular na adolescência. Observou-se ausência de associação entre o baixo peso ao nascer e adversos resultados de saúde entre os adolescentes com baixo nível socioeconômico de um centro urbano no Nordeste brasileiro.

Introduction

Over the past two decades, an extensive and growing literature has investigated the associations between low birth weight (LBW) and chronic diseases. Several clinical studies demonstrate that LBW is an important risk factor for atherosclerosis, type 2 diabetes, hypertension, metabolic syndrome and endothelial dysfunction.^{1–8} Many of those studies were conducted in countries with high average socioeconomic status and the majority demonstrated a strong association between LBW and increased risk of cardiovascular disease.

Nevertheless, many other studies have only found a positive or a non-association between LBW and cardiovascular disease risk factors in young men and women or in children and adolescents. Moreover, there is convincing evidence that postnatal weight gain may have a greater influence on blood pressure than birth weight.^{4,9–11}

There are not many studies of cardiovascular risk factors for LBW pediatric populations in the Brazilian northeast.^{12,13} This region has the lowest average socioeconomic status and the highest under-five mortality rates when compared with the other regions of the country.¹⁴ In recent years, the Brazilian government has invested heavily in programs in the northeast to ensure better child nutrition. However, these increases in the population's income have not been reflected in health indicators, and the prevalence of overweightness and obesity (important predictors for several cardiovascular disease risk factors) is rising.¹⁵

The hypothesis of this study is that LBW adolescents in low average socioeconomic status regions have the poorest

health status. Thus, the research was conducted to investigate whether LBW is associated with changes during adolescence in anthropometric and biochemical risk factors, in a low average socioeconomic status population in the Brazilian northeast.

Methods

We conducted a retrospective cohort study with male and female participants with ages varying from 10 to 20 years, born from 1992 to 2002, with LBW (less than 2,500 g at birth) or normal birth weight (NBW) ($\geq 2,500$ g) and who were born and lived in Fortaleza, Brazil. This study was approved by The Research Ethics Committee of the Assis Chateaubriand Maternity Teaching Hospital and conducted between February and August 2013. A similar sample size was applied in previous studies which assessed the endothelial and metabolic disorders and fetal growth restriction in adolescents.^{16,17}

Hospital birth records were used to check perinatal conditions and select potential subjects. Eligibility criteria included being healthy at the moment of the evaluation and having no cardiovascular and/or endocrine conditions or relevant cardiovascular disease risk factors. Participants were contacted through personal visits, phone calls and letters.

A total of 101 LBW adolescents were located; however, the mothers of 15 of these adolescents refused to sign the consent for the adolescent's participation in the study. As for the NBW group, 102 adolescents were located,

with the mothers of 16 of them refusing to sign the consent.

The evaluation consisted of an interview to investigate medical history and familial occurrence of cardiovascular disease risk factors, and to conduct laboratorial exams and anthropometric and clinical measurements.

Weight and total body fat percentage, with the participants wearing light clothes and no shoes, were measured to the nearest 0.1 kg / 0.1% using a calibrated model W835 body analyzer (Wanchai-Ho, China). A wall-mounted stadiometer Seca (model 206, Hamburg, Germany) to the nearest 0.1 cm was used to measure standing height. With these measurements the body mass index (BMI) was calculated (in kilograms per square meters) and evaluated according to age and gender, based on World Health Organization (WHO) references.¹⁸

An anthropometric tape measure Wiso (model T872) was used to measure the circumference of the waist, abdomen and hips. The measurements were taken at the end of a gentle expiration, with the reference point halfway between the lower rib and the top of the iliac crest; the umbilical scar and the largest point of the outer hip, respectively. Other two measurements were waist/hip ratio and biceps skinfold were also measured.

To measure blood pressure, a Microlife calibrated semi-automatic sphygmomanometer (model BP 3BTO-H, Dunedin, USA) was used, after a 30-minute rest, and giving a 1-minute interval between the two measurements. If the difference between the first and second measurements was ≥ 20 mm Hg, a new one would be taken, and the average of the two closest measurements was used as the final result. The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and

Adolescents was used as a reference for blood pressure according to age and gender.¹⁹

For laboratorial evaluation, fasting blood sugar test samples were collected, as well as samples to measure total cholesterol, high-density lipoprotein cholesterol and triglycerides. Low density lipoprotein cholesterol was calculated when triglycerides < 400 mg/dL.²⁰ The I Guideline for Prevention of Atherosclerosis in Childhood and Adolescence was adopted as reference value.¹⁰ Each participant received their laboratory results and a cardiovascular report.

Statistical Analysis

Mean and standard deviations were calculated to all normality variables using Student's t test, and proportions were compared by Chi-square (χ^2) or Fisher exact tests. Kruskal-Wallis and Mann-Whitney U tests were used for non-normal distribution variables and described as quartiles: first quartile (Q1), median (M) and third quartiles (Q3). Some variables were converted to Z-score by using the formula: $(x - \text{mean})/\text{standard deviation}$. Analysis were performed using Stata program (College Station, TX, USA) version 12.0 for Mac and statistically significant if $p < 0.05$. An alpha error of 5% and a beta error of 20% were adopted to calculate the sample size according to a relative risk of 2.3 to hypertension in preterm and low birth weight subjects.²¹

Results

Evaluations were obtained from 86 LBW and 86 NBW participants. The sample consisted of 56 females (65.1%) in the

Table 1 Maternal characteristics during childbirth according offspring's birth weight

	LBW Q1 (M) Q3		NBW Q1 (M) Q3		p
Age (years)	18.0 (24.5) 30.0		20.0 (23.0) 28.0		0.5*
Pregnancy complications (n,%)					
Preeclampsia	32	37.2	23	26.7	$< 0.001^\dagger$
Diabetes	2	2.3	0	0.0	
Other diseases	43	49.9	13	15.2	
Mode of delivery (n,%)					
Vaginal	45	52.3	32	37.2	$< 0.05^\S$
Cesarean	41	47.7	54	62.8	
Number of pregnancies	0.8 ± 1.2		1.4 ± 2.7		0.2*
Number of births	0.6 ± 0.9		0.9 ± 1.8		0.5*
Number of abortions	0.2 ± 0.5		0.5 ± 1.3		0.3*
Complications in other pregnancies (n,%)	22	25.6	20	23.3	0.4§
Smoking (n,%)	2	2.4	8	9.6	0.1§

Abbreviations: LBW, low birth weight; M, median; NBW, normal birth weight; Q1, first quartile; Q3, third quartile.

Note: Values are median and interquartile range for continuous variables; number of participants and percentages are presented for categorical variables however.

*Mann-Whitney U test, † Fisher's exact, § Chi-square (χ^2) test.

Table 2 Perinatal, anthropometric, and clinical current data according to birth weight groups

	LBW Q1 (M) Q3		NBW Q1 (M) Q3		p
Gender					
Boys (n,%)	30	34.9	34	39.5	0.5 [†]
Girls (n,%)	56	65.1	52	60.5	
SGA (n,%)	49	57.0	9	10.5	< 0.001 [†]
Current data					
Age (years)	11.0 (12.0) 14.0		11.0 (13.0) 16.0		0.2*
Weight (kg)	40.2 (47.7) 56.7		40.6 (49) 58.5		0.8*
Z-score weight	-0.01 ± 1.0		0.01 ± 1.0		0.8 [§]
Height (m)	1.5 (1.5) 1.6		1.5 (1.6) 1.6		0.1*
Z-score height	-0.1 ± 1.0		0.1 ± 1.0		0.1 [§]
Abdominal circumference (m)	0.6 (0.7) 0.8		0.6 (0.7) 0.8		0.6*
Z-score abdominal circumference	0.02 ± 1.0		-0.02 ± 1.0		0.6 [§]
Hip circumference (m)	0.6 (0.7) 0.8		0.6 (0.7) 0.7		0.8 [§]
Z-score hip circumference	0.03 ± 1.0		-0.03 ± 1.0		0.5 [§]
Waist/hip ratio	0.8 (0.8) 0.8		0.7 (0.8) 0.8		0.2*
Z-score waist/hip ratio	0.1 ± 0.1		-0.1 ± 0.1		0.1 [§]
BMI (mean)	17.6 (20.1) 23.9		17.5 (19.9) 23.1		0.8*
Z-score BMI	0.46 ± 1.0		-0.46 ± 1.0		0.5 [§]
Classification according to BMI					
Overweightness/obesity (n,%)	23	26.8	23	26.8	0.5 [†]
Normal (n,%)	54	62.8	55	64.0	
Body fat mass (%)	20.9 (26.5) 35.2		20.7 (25.2) 33.3		0.4*
Z-score body fat mass	0.1 ± 0.1		-0.1 ± 0.1		0.4 [§]
Biceps skinfold thickness (m)	0.005 (0.007) 0.011		0.005 (0.007) 0.009		0.6*
Z-score biceps skinfold thickness	0.05 ± 1.0		-0.05 ± 1.0		0.6 [§]
SBP (mmHg)	97 (108) 110		90 (100) 108		0.1*
Z-score SBP	0.1 ± 0.1		-0.1 ± 0.1		0.1 [§]
PAS ≥ 95 th percentile	9	10.5	9	10.5	0.9 [†]
DBP (mmHg)	60 (65) 70		58 (63.5) 67		0.1*
Z-score DBP	0.1 ± 1.1		-1.1 ± 0.8		0.1 [§]
PAD ≥ 95 th percentile	1	1.2	0	0	0.1 [†]
Family history of CVD ^f					
Yes (n,%)	83	96.5	78	90.7	0.1 [†]
No (n,%)	3	3.5	8	9.3	
Menarche age	11 (11) 12		11 (12) 13		0.2*
Familiar incomes (MW)	1 (1.5) 2		1 (1) 2		0.8*
Maternal school education (years)	5 (8.5) 11		5 (8) 11		0.8*

Abbreviations: BMI, body mass index (in kilograms per square meters); CVD, cardiovascular disease; DBP, diastolic blood pressure; LBW, low birth weight; M, median; MW, minimum wage; NBW, normal birth weight; Q1, first quartile; Q3, third quartile; SBP, systolic blood pressure; SGA, small for gestation age.

Note: Values are median and interquartile range for continuous variables; number of participants and percentages are presented for categorical variables however.

*Mann–Whitney U test, [†]Chi-square test (χ^2) test, [§]Student's t-test.

Table 3 Blood lipids and insulin profile according to birth weight groups

	LBW	NBW	p*
Glucose (mg/dL)	79.7 (9.6)	82.3 (9.5)	0.2
TC (mg/dL)	143.0 (24.4)	143.4 (26.2)	0.9
HDL-C (mg/dL)	43.4 (10.2)	44.3 (10.1)	0.5
LDL-C (mg/dL)	84.6 (21.1)	84.4 (23.6)	0.7
VLDL (mg/dL)	14.6 (6.5)	13.9 (7.1)	0.4
TG (mg/dL)	73.0 (32.6)	70.9 (30.0)	0.5

Abbreviations: HDL-C, high-density lipoprotein cholesterol; LBW, low birth weight; LDL-C, low-density lipoprotein cholesterol; NBW, normal birth weight; TC, total cholesterol; TG, triglycerides; VLDL-C, very low-density lipoprotein cholesterol.

Note: Values are mean and standard variation.

*Mann-Whitney U test.

LBW group and 52 females (60.5%) in the NBW group ($p = 0.5$), with an average age of 12.8 years for LBW ($SD = 2.2$) and 13.6 years for NBW ($SD = 2.9$) ($p = 0.2$). Of the total of 58 adolescents born small for gestational age, 49 (57.0%) were also LBW ($p < 0.05$).

The maternal characteristics were similar, except for the mode of delivery ($p < 0.05$) (►Table 1). No significant differences were identified regarding age, gender distribution, or current anthropometric data (weight, height, abdominal circumference, BMI, classification according to BMI, body fat mass and biceps skinfold thickness) (►Table 2). The clinical parameters were similar between the groups. Systolic blood pressure and diastolic blood pressure levels were also similar in the LBW group (systolic blood pressure = 2.6 mm Hg; diastolic blood pressure = 1.5 mm Hg). Subjects in the LBW group tended to have lower height ($p = 0.1$). No differences were found in the family history of cardiovascular diseases ($p = 0.1$), family incomes ($p = 0.7$) or maternal schooling ($p = 0.8$). We also expressed anthropometric variables as mean Z-scores. No significant differences were found. All the values were expressed as mean and standard deviations (►Table 2).

The data from the biochemical evaluation showed very similar results between LBW and NBW participants. Although low-density lipoprotein cholesterol, very low-density lipoprotein cholesterol and triglycerides levels were higher in the LBW group, there was no significant difference. Similarly, even though total cholesterol, high-density lipoprotein cholesterol and glucose levels were higher in the NBW group, no significant differences were observed (►Table 3).

Because more than 50% of the eligible patients were lost, we performed some statistical tests between participants and non-participants. LBW participants and non-participants had similar performances regarding perinatal characteristics such as maternal age ($p = 0.4$), number of maternal gestations and abortions ($p = 0.5$; $p = 0.8$ respectively), maternal preeclampsia and diabetes ($p = 0.5$; $p = 0.2$ respectively), age (the average age of participants was 13, and the average age of non-participants was 12; $p < 0.05$), gender ($p = 0.7$), prematurity ($p = 0.1$), small size for gestational age (higher frequency of

adolescents born small for gestational age in the participant's group, $p < 0.05$).

Discussion

The findings presented suggest that low birth weight was not associated with poor health outcomes among adolescents in the Brazilian northeast. The differences were non-significant for all risk factors except for blood pressure, where a borderline significant difference was observed. The adolescents in the LBW group had higher blood pressures (2.6 mm Hg for systolic blood pressure and 1.5 mm Hg for diastolic blood pressure), and they tended to have lower height than adolescents in the NBW group. These three variables showed the highest difference in the anthropometric data and tended to be higher in the LBW group, but were not significant. Although we selected subjects born on the same day, from 1992 to 2002, the groups had a different quartile of age. This occurred because we couldn't localize the adolescents born exactly on the same day. However, this didn't affect the results.

One of the strongest predictors of hypertension in adulthood is a high level of blood pressure in childhood.²² Another important risk factor is gender, which may influence the probability of elevated blood pressure during adulthood.²³ Among women, the risk ratio ranged from 2.6 to 5.7, while among men it ranged from 2.3 to 4.3. However, some studies have found opposite results. A longitudinal prospective study with 250 subjects with ages between 11 and 14 years found no correlation between birth weight and blood pressure, weight or BMI. The authors suggested there are risk factors more important than LBW or gestational age that are related to increased blood pressure in childhood, such as high maternal BMI and a high birth weight (HBW).²⁴

In Iceland, a study²⁵ investigated 857 children with ages between 9 and 10 years, 51.9% of which were girls. They found higher blood pressure levels among the boys, but no correlation was found between birth weight and absolute blood pressure values. Gestational age also did not correlate with blood pressure. Studies with other populations had

similar results in the US,²⁶ China,⁹ England,⁴ Italy²⁷ and Brazil.²⁸

Despite socioeconomic factors such as family incomes and maternal education being comparable, the LBW group did not have an increased risk of cardiovascular disease. Studies show that women who deliver LBW infants take meticulous care of them and pay closer attention to medical advices.²⁹ This could be the reason for less cardiovascular disease risk factors associated with catch-up growth,³ a determinant factor for cardiovascular diseases in LBW newborns. On the other hand, Fortaleza currently ranks as the ninth worst Brazilian capital on the Municipal Human Development Index.³⁰ This index encompasses longevity, education and income. Thus, in this study NBW newborns were also exposed to poor conditions, which may explain why their results were similar to those of LBW newborns, even though the groups had a similar family history of cardiovascular diseases.

Countries have some peculiarities regarding socioeconomic status. It has been estimated that in regions in the world with low average socioeconomic status more than 200 million children less than 5 years old are not fulfilling their development potential. This fact can be the result of poverty, nutritional deficiencies and inadequate learning opportunities.³¹ In Brazil specifically, there have been fast changes in major social health determinants and in the organization of health services over the past three decades. The main changes during this period were economic growth, reduction in income inequality, urbanization, improvements in the education of women, decreased fertility rates, a government cash transfer program and improvements in the provision of water and sanitation.³²

Furthermore, since the 1970's a nutritional transition is occurring in Brazil, involving a decline in malnutrition in children and an increase in obesity and overweightness in adults. It is an apparent paradox that the highest frequencies of normal anthropometric measurements in Brazilian adults were found in the poorer northern and northeastern regions of Brazil.³³ However, a recent study showed that cardiovascular disease increased in these regions.³⁴

The results contribute toward testing the validity of the Barker hypothesis in countries with low average socioeconomic status, especially in the poorest region of Brazil. An important feature in this study is that socioeconomic status and the same day of birth were accounted for and the groups were similar in average chronological age, gender and time frame for the menarche. We used international parameters to facilitate future comparisons with our data.

Some study limitations need to be addressed. Firstly, the neonatal data obtained from the hospital records had only been collected prior to the present study for other purposes and a long time ago. For that reason, some data was missing. Secondly, adolescents with birth weight between 2,500 and 3,000 g ($n = 25$) were included in the NBW group; however, this group could include some subjects who did not reach their potential for intrauterine growth, which lead to confusing results. Although some authors

categorized birth weight in a manner similar to this research, they had different results.³⁵ Thirdly, complete information regarding pubertal status was not available, so bias may have been introduced by giving all participants the same pubertal status. Fourthly, we can't increase our sample. As we have described, there were some difficulties in obtaining the hospital records that have maternal and neonatal data. Despite this, we got more than one thousand records. Unfortunately, we were unable find most of the patients. However, as we have shown, participants and non-participants had similar characteristics, and non-participants were not the reason behind the few differences between the groups that we found. Fifthly, we based our sample size calculation on hypertension; however a few number of subjects had high levels of blood pressure. This could be the reason why no other differences were found.

Summarizing, LBW did not increase cardiovascular disease risk factors in young adults in the second decade of life. The absence of an association between LBW and poor health outcomes among adolescents in a low average socioeconomic status population from a capital in the Brazilian northeast corroborates previous findings in other countries with low average socioeconomic status. We suggest future prospective studies with more subjects to investigate this association.

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